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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,245	12/18/2001	Yoshiaki Fukuda	46/224	8337

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EXAMINER

GAMBEL, PHILLIP

ART UNIT PAPER NUMBER

1644

DATE MAILED: 04/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/018,245	FUKUDA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 14-23 is/are pending in the application.
- 4a) Of the above claim(s) 18-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date. _____   | 6) <input type="checkbox"/> Other: _____                                    |

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**Detailed Action**

1. Applicant's amendment, filed 2/3/05, has been entered.  
Claims 1-13 have been canceled.  
Claims 14-23 have been added.
2. Applicant's election with traverse of Group I (claims 14-18) is acknowledged. The traversal is on the ground(s) that the presently pending claims constitute one invention and thus no restriction requirement should be imposed.

As pointed out in the previous Office Action, mailed 10/4/04. The inventions previously listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I-IV were found to have no special technical feature that defined the contribution over the prior art of Nagahira et al. (J. Immunol. Methods 222: 83-92 (1999), Nagahira et al. Immuno. Lett. 64: 139-144 (1998) and Hirai et al. (J. Immunol. Methods 96: 57-62 (1987) as set forth in International Search Report provided in the instant application.

Accordingly, Groups I-IV were not so linked by the same or a corresponding special technical feature as to form a single general inventive concept that defines a contribution over the prior art.

Also, the inventions require non-coextensive searches.

Given applicant's canceled and newly presented claims, the following Groups apply to the pending claims.

Group I, claims 14-17, drawn to recombinant anti-TNF $\alpha$  antibodies and compositions thereof.

Group II, claims 18-23, drawn to genes, expression vectors and methods of producing recombinant anti-TNF $\alpha$  antibodies.

Claims 14-17 are under consideration as they read on the elected invention.

Claims 18-23 have been withdrawn as they read on a non-elected invention.

2. While it appears that applicant is in compliance with the Sequence Rules, applicant is required to review the instant application for compliance with the requirements of an application which contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825.

If the instant application does not have an appropriate SEQ ID NO: for each disclosed sequence, then applicant must comply with the Sequence Rules as set forth in 37 CFR 1.821-1.825.

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For example, the Abstract and the Brief Description of Drawings (see Figure 1) refer to sequences, but they do not disclose the appropriate SEQ ID NOS.

Applicant is required to review the entire instant application to make sure that the instant application is in compliance with the Sequence Rules.

3. The priority date of the instant application appears to be the priority date of PCT/JP01/03308, filed 4/18/01.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the <sup>TM</sup> or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The Brief Description of the Drawings must be amended to recite the different part numbers of the drawings. For example, Figure 1 should be Figure 1A-B.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant TNF $\alpha$ -specific antibodies and antigen-binding fragments thereof, in which the three (3) CDRs in the heavy chain variable region and the three (3) CDRs in the light chain variable region are all defined by a single antibody, and which bind the relevant antigen (human TNF $\alpha$ );

does not reasonably provide enablement for antibodies and antigen-binding fragments thereof that comprise *less than three* heavy chain CDRs and the three light chain CDRs defined by the amino acid sequence of the humanized 3B10I antibody that binds human TNF $\alpha$

or "an amino acid sequence derived from said amino acid sequence by deletion, addition, or substitution of one to several amino acids in a region other than the amino acid sequences represented by SEQ ID NOS: 1 to or 3 or its fragment".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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The breadth of the claims encompass antibodies in which fewer than all of the six (6) CDRs found in the heavy plus light pair that forms the binding region of a humanized 3B10 TNF $\alpha$ -specific antibodies are defined.

Although a limited number of changes are made to the humanized 3B10 antibody domains (e.g. the mutations described in the Examples), these changes are made in the context of a total of six (6) CDRs in humanized 3B10 anti-human TNF $\alpha$  antibodies.

The state of the art recognized that all three (3) CDRs of the heavy chain variable region and all three (3) CDRs of the light chain variable region were important for determining the ability of the antibody to bind antigen.

For example, <sup>Bendig</sup>~~Bending~~ (Methods: A Companion to Methods in Enzymology 8: 83-93, 1995) reviews the general strategy for "humanizing" antibodies involves the substitution of all six (6) CDRs from a rodent antibody that binds an antigen of interest, and that all six (6) CDRs are involved in antigen binding (see entire document, including Figures 1-3).

While the instant recombinant antibodies are fully humanized, the same considerations apply to the genus of recombinant antibodies defined only based upon a single heavy and/or light CDR sequence.

Thus, the state of the art recognized that it would be highly unpredictable that an antibody comprising less than all six (6) CDRs from an antibody with a desired specificity would bind the same antigen. Thus the minimal structure which provides the function of human TNF $\alpha$ -specific binding appears to include six (6) CDRs (three (3) in the heavy chain variable region and three (3) in the light chain variable region) from the humanized 3B10 anti- TNF $\alpha$  antibodies.

Further, applicant's instant specification (e.g. page 12, lines 8-19 and Example 3) appear to acknowledge that all six (6) CDRs are required for the recited function of recombinant antibodies that bind human TNF $\alpha$ .

In addition, the skilled artisan recognized that single CDRs with the same amino acid sequences can be found in antibodies with diverse specificities. In particular, antibodies which have not yet undergone affinity maturation may still utilize germline heavy and light chain sequences. Between antibodies utilizing the same germline heavy or light chain gene, the skilled artisan would expect to find that one or more of the heavy and/or light chain CDRs were the same as that of an antibody with a different specificity. Also, the same CDR may occur in antibodies having somatic mutations or engineered antibodies that bind different antigens.

For example, Baca et al. (WO 98/45331) describes recombinant anti-VEGF antibodies that comprise the same SEQ. ID. NO: 1 as claimed (see entire document, including SEQ ID NO: 2 set forth in claim 6).

Thus, it would be unpredictable that an antibody comprised of fewer than all six (6) CDRs (three CDRs defined in the heavy chain variable region and three (3) CDRs defined in the light chain variable regions) of a particular reference antibody would have the same specificity as the reference antibody.

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Further, the claims encompass more variability and unpredictability, given the recitation of "fragments of heavy / light chain polypeptides" and "an amino acid sequence derived from said amino acid sequence by deletion, addition, or substitution of one to several amino acids in a region other than the amino acid sequences represented by SEQ ID NOS: 1 to or 3 or its fragment" in the absence of sufficient guidance and direction as to those amino acids that provide the appropriate structure and specificity for humanized anti-human TNF $\alpha$  antibodies based upon the 3B10 antibody.

The specification as filed does not appear to provide any working examples that fewer than all six (6) CDR s are required for binding to human TNF $\alpha$ . Neither does the specification appear to provide sufficient guidance; it would require undo experimentation of the skilled artisan to make antibodies which could bind human TNF $\alpha$  and satisfy the disclosed utilities that comprised fewer than all six (6) CDRs from a humanized 3B10 anti-human TNF $\alpha$  antibodies.

Reasonable correlation must exist between the scope of claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having fewer than all six (6) CDRs from a reference antibody as well as a number of amino acid modifications and the lack of sufficient guidance provided in the specification, the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

8. Claims 14-17 are objected to in that applicant is invited to amend the claims to clearly recite an "antibody that binds" (or alternative appropriate language) rather than the ill-described "antibody against", as currently recited, for clarity.

Claims 14-17 are objected to because the abbreviation "H" and "L" should be defined or spelled out at least upon first time usage in the claims for clarity.

9. Claims 14-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-17 are indefinite in the recitation of "or its fragment", because the antecedent basis of the fragment is unclear and ambiguous. For example, "its fragment" could read on "antibody", "TNF  $\alpha$ ", "polypeptide", "SEQ ID NOS: 1 or 3 / SEQ ID NOS 4 or 6".

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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11. Claims 14-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nagahira et al. (J. Immunological Methods 222: 83-92 (1999) (1449; #RR) (see entire document).

Nagahira et al. teach the same or nearly the same humanization of the same neutralizing anti-human TNF $\alpha$  3B10 antibody, as disclosed in the instant application and claimed (e.g. see Abstract, Materials and Methods, Results, including Figures 1 and 2 as well as Table 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed structural limitations would be inherent properties of the referenced humanized 3B10 anti-human TNF $\alpha$  3B10 antibodies. The burden is on the applicant to establish a patentable distinction between the claimed and referenced humanized 3B10 anti-human TNF $\alpha$  3B10 antibodies.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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April 4, 2005